

N isomer

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(54) Title: S-LANSOPRAZOLE COMPOSITIONS AND METHODS (57) Abstract <p>Methods and compositions are disclosed utilizing optically pure (-) lansoprazole for the treatment of ulcers in humans while substantially reducing the concomitant liability of adverse effects associated with the racemic mixture of lansoprazole. The optically pure (-) isomer is also useful for the treatment of gastroesophageal reflux. (-) Lansoprazole is an inhibitor of H⁺ release and is therefore useful in the treatment of other conditions related to gastric hypersecretion such as Zollinger-Ellison Syndrome.</p>			

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S-LANSOPRAZOLE COMPOSITIONS AND METHODS

FIELD OF THE INVENTION

This invention relates to compositions of matter containing lansoprazole. The invention also relates to methods of treating and preventing ulcers, treating other conditions related to gastric hypersecretion, and treating psoriasis.

BACKGROUND OF THE INVENTION

Racemic lansoprazole is an orally active, potent, irreversible inhibitor of H^+, K^+ -ATPase. The compound is one of the class of compounds known as gastric "proton pump" inhibitors. These compounds are weak organic bases which diffuse passively from the plasma into the acid-containing intracellular canaliculi of gastric parietal cells. At the low pH found in the lumen of these canaliculi, the protonated compounds rearrange to form pyridinium sulfenamides, which react with sulfhydryl groups present on the ATPase localized in the membranes lining the intracellular canaliculi. The alkylation of the sulfhydryl inhibits the ability of the enzyme to catalyze the secretion of H^+ into the lumen in exchange for K^+ ions. This inhibition results in an overall reduction in hydrochloric acid secretion by the parietal cells into the cavity of the stomach, thus increasing intragastric pH. As a consequence of reduced acidity in the stomach, the activity of the proteolytic enzyme pepsin is also markedly decreased. Because the proton pump is the final step in acid

production and the compounds of this class combine covalently with the associated H^+, K^+ -ATPase, a profound and prolonged inhibition of gastric acid secretion can be achieved.

5 Proton pump inhibitors have also been reported as useful in treating psoriasis. [See PCT application WO95/18612]

10 The C_{max} of racemic lansoprazole is at about 1.7 hours in humans and the serum half-life is about 1.5 hours, but this does not reflect the duration of the acid inhibitory effect, which is about 24 hours.

Racemic lansoprazole is comparable to omeprazole in its effects on hepatic drug metabolizing enzyme systems.

15 Although no cardiovascular or obvious physical sequelae of elevated gastrin have been observed in humans on administration of racemic lansoprazole, fasting serum gastrin levels are significantly elevated. This is cause for concern because
20 prolonged elevated serum gastrin appears to be associated with diffuse and focal enterochromaffin-like cell hyperplasia and focal neoplasia (carcinoids) in rats. [Larsson et al. Gastroenterology 90, 391-399 (1986)]. Thus, despite
25 its advantages, adverse effects of racemic lansoprazole may remain, including, but not limited to, some incidence of hepatocellular neoplasia and gastric carcinoids on long-term therapy, and headache, diarrhea and skin alterations on acute
30 therapy. There has also been some concern about the

inhibition of cytochrome P450 enzymes by racemic lansoprazole [Kromer Digestion 56, 443-454 (1995)]; this effect would lead to adverse drug-drug interactions.

- 5 The following adverse events have been reported in lansoprazole-treated patients: Body as a Whole - asthenia, candidiasis, chest pain (not otherwise specified), edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise;
- 10 Cardiovascular System - angina, cerebrovascular accident, hypertension/hypotension, myocardial infarction, palpitations, shock (circulatory failure); vasodilation; Digestive System - melena, anorexia, bezoar, cardiospasm, cholelithiasis,
- 15 constipation, dry mouth/thirst, dyspepsia, dysphagia, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastroenteritis, gastrointestinal hemorrhage, hematemesis, increased
- 20 appetite, increased salivation, rectal hemorrhage, stomatitis, tenesmus, ulcerative colitis, vomiting; Endocrine System - diabetes mellitus, goiter, hyperglycemia/hypoglycemia, Hematologic and Lymphatic System - anemia, hemolysis; Metabolic and Nutritional
- 25 Disorders - gout, weight gain/loss; Musculoskeletal System - arthritis/arthralgia, musculoskeletal pain, myalgia; Nervous System - agitation, amnesia, anxiety, apathy, confusion, depression, dizziness/syncope, hallucinations, hemiplegia,
- 30 aggravated hostility, decreased libido, nervousness, paresthesia, thinking abnormality; Respiratory System - asthma, bronchitis, cough increased, dyspnea,

epistaxis, hemoptysis, hiccup, pneumonia, upper
respiratory inflammation/infection; Skin and
Appendages - acne, alopecia, pruritis, rash,
urticaria, Special Senses - amblyopia, deafness, eye
5 pain, visual field defect, otitis media, taste
perversion, tinnitus; Urogenital System - abnormal
menses, albuminuria, breast enlargement/gynecomastia,
breast tenderness, glycosuria, hematuria, impotence,
kidney calculus.

10 It would therefore be particularly desirable to find
a compound with the advantages of the racemic mixture
of lansoprazole which would not have the
aforementioned disadvantages.

SUMMARY OF THE INVENTION

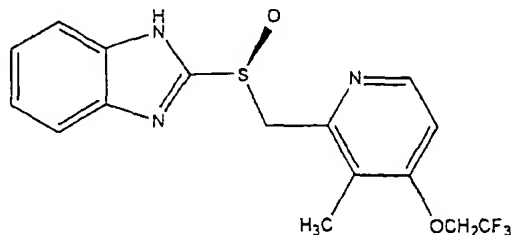
15 This invention relates to the use of optically
pure S(-)lansoprazole for treating ulcers of the
stomach, duodenum and esophagus, gastroesophageal
reflux diseases, Zollinger-Ellison Syndrome, and
other disorders including those that would benefit
20 from an inhibitory action on gastric acid secretion.
S(-)Lansoprazole inhibits the H⁺, K⁺-ATPase associated
with the gastric proton pump and the resulting
secretion of gastric acid by parietal cells providing
therapy in diseases associated with gastric
25 hyperacidity. The invention also relates to a
method of treating psoriasis using optically pure
S(-) lansoprazole. Optically pure (-) lansoprazole
provides this treatment while substantially reducing
adverse effects, including, but not limited to,

hepatocellular neoplasia, gastrin hypersecretion,
gastric neoplasms or carcinoids, headache, diarrhea
and skin alterations which are associated with the
administration of the racemic mixture of
5 lansoprazole.

The invention also relates to certain oral
pharmaceutical compositions containing the S(-)
isomer of lansoprazole.

DETAILED DESCRIPTION OF THE INVENTION

10 The active compound of these compositions and
methods is an optical isomer of lansoprazole. The
preparation of racemic lansoprazole is described in
United States Patents 4,628,098 and 4,689,333. The
medicinal chemistry and clinical aspects of racemic
15 lansoprazole have been reviewed by Garnett [Ann.
Pharmacother. 30, 1425-1436 (1996)], by Langtry and
Wilde [Drugs 54, 473-500 (1997)] and by Barradell et
al. [Drugs 44, 225-250 (1992)]. Chemically, the
active compound is the (-) isomer of 2-[3-methyl-4-
20 (2,2,2-trifluoroethoxy)pyrid-2-yl]methylsulfinyl-
benzimidazole(I), hereinafter referred to as
lansoprazole.



I

(-) Lansoprazole, which is the subject of the present invention, is not presently commercially available; only the 1:1 racemic mixture is commercially available as Prevacid®.

5 Syntheses of R (+) lansoprazole and S (-) lansoprazole by asymmetric oxidation and by bioreduction are described in PCT applications WO 9602535 and 9617077, respectively, the disclosures of which are incorporated herein by reference. The
10 enrichment of single enantiomers by crystallization of the racemate from non-racemic mixtures is described in PCT application WO 97/02261, the disclosure of which is also incorporated herein by reference.

15 The pharmacology of the individual enantiomers in canine parietal cells and gastric microsomes has been reported by Nagaya et al. [Biochem. Pharmacol. 42, 1875-1878 (1991)], who concluded that "the effects of the (+) and (-) enantiomer of lansoprazole
20 on acid formation stimulated by db-cAMP in isolated parietal cells were almost identical." Similarly, inhibition of ATPase activity in gastric microsomes by the two enantiomers did not differ significantly over the range of concentrations tested.

25 It has now been discovered that the optically pure (-) isomer of lansoprazole is a superior agent for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome, psoriasis and other

disorders, including those that would benefit from an inhibitory action on H^+, K^+ -ATPase in that it provides this effective treatment while substantially reducing the adverse effects of racemic lansoprazole including, but not limited to, hepatocellular neoplasia, gastric carcinoids, headache, diarrhea and skin alterations. The S(-) isomer of lansoprazole is also a superior agent for treating ulcers and other disorders by virtue of its lessened liability for drug-drug interactions and its greater predictability of dosage among patients, as discussed below. Surprisingly, it also shows a longer duration, a higher AUC (area under the curve - a composite measure of efficacy and duration), and a more rapid onset as a result of lower first pass metabolism.

The present invention encompasses a method of treating ulcers, which comprises administering to a human in need of such therapy, an amount of (-) lansoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, said amount being sufficient to alleviate the symptoms of ulcers. The method substantially reduces the concomitant liability of adverse effects associated with the administration of the racemic compound by providing an amount which is insufficient to cause the adverse effects associated with the racemic mixture of lansoprazole.

The present invention also encompasses an oral antiulcer composition for the treatment of a human in need of antiulcer therapy, which comprises a pharmaceutically acceptable carrier for oral

administration and a therapeutically effective amount of (-) lansoprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer. Preferably the composition is in the form of a tablet or capsule and the amount of (-) lansoprazole in the tablet or capsule is 15, 30 or 60 mg.

The present invention further encompasses a method of treating gastroesophageal reflux disease and of treating conditions caused by or contributed to by gastric hypersecretion. Conditions associated with hypersecretion in humans may include, but are not limited to, Zollinger-Ellison syndrome.

The present invention further encompasses a method of treating psoriasis while substantially reducing the adverse effects of racemic lansoprazole.

Utilizing the optically pure or substantially optically pure isomer of (-) lansoprazole results in enhanced efficacy, diminished adverse effects, and accordingly, an improved therapeutic index. It also provides more rapid onset and longer duration of the therapeutic effect. Moreover, the S(-) enantiomer exhibits fewer drug-drug interactions and shows less variation in the patient population between so-called good metabolizers and poor metabolizers. It is therefore, more desirable to use the (-) isomer of lansoprazole than to administer the racemic mixture because predictability of an effective and safe dose for an individual patient is greater. The S(-) enantiomer of lansoprazole is metabolized by both

CYP2D6 and CYP3A4; the R(+) enantiomer is metabolized only by CYP2D6, which is the polymorphically expressed enzyme. Because it is metabolized by both enzymes, the S(-) shows less variability in the
5 patient population and a more predictable dosage regimen. Surprisingly, the S(-) isomer also shows a longer duration, a higher AUC and a more rapid onset as a result of lower first pass metabolism.

The term "adverse effects" includes, but is not
10 limited to, hepatocellular neoplasia, gastrin hypersecretion, gastric carcinoids, headache, diarrhea, skin alterations and drug-drug interactions.

The term "substantially free of its (+)
15 stereoisomer" as used herein means that the compositions contain at least 90% by weight of (-) lansoprazole and 10% by weight or less of (+) lansoprazole. In a more preferred embodiment the term "substantially free of the (+) isomer" means
20 that the composition contains at least 99% by weight of (-) lansoprazole, and 1% or less of (+) lansoprazole. These percentages are based upon the total amount of lansoprazole in the composition. The terms "substantially optically pure (-) isomer of
25 lansoprazole" or "substantially optically pure (-) lansoprazole" and "optically pure (-) isomer of lansoprazole" and "optically pure (-) lansoprazole" are also encompassed by the above-described amounts.

The term "treating ulcers" as used herein means
30 treating, alleviating or palliating such conditions,

and thus providing relief from the symptoms of nausea, heartburn, post-prandial pain, vomiting, and diarrhea.

5 The term "a method for treating gastroesophageal reflux diseases in a human" as used herein means treating, alleviating or palliating the conditions that result from the backward flow of the stomach contents into the esophagus.

10 The term "treating a condition caused, or contributed to, by gastric hypersecretion in a human" as used herein means treating, alleviating or palliating such disorders associated with hypersecretion, thus providing relief from the symptoms of the aforementioned conditions.
15 Zollinger-Ellison Syndrome is among the conditions caused by or contributed to by hypersecretion.

The term "treating psoriasis" as used herein means treating, alleviating or palliating the condition, and thus providing relief from the
20 symptoms of pruritis, epidermal scaling, itching and burning.

The magnitude of a prophylactic or therapeutic dose of (-) lansoprazole in the acute or chronic management of disease will vary with the severity of
25 the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for (-)

lansoprazole for the conditions described herein is from about 10 mg to about 180 mg in single or divided doses. Preferably a daily dose range should be about 15 mg to about 60 mg in single or divided doses. In
5 managing the patient, the therapy should be initiated at a lower dose, perhaps at about 10 mg to about 15 mg and increased up to about 60 mg or higher depending on the patient's global response. It is further recommended that children and patients over
10 65 years and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to
15 those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "an amount sufficient to alleviate or palliate
20 ulcers but insufficient to cause said adverse effects," "an amount sufficient to alleviate the symptoms of gastroesophageal reflux but insufficient to cause said adverse effects," "an amount sufficient to alleviate gastric hypersecretion but insufficient
25 to cause said adverse effects" and "an amount sufficient to treat psoriasis" are encompassed by the above-described dosage amounts and dose frequency schedule.

The relative activity, potency and specificity
30 of optically pure lansoprazole and racemic lansoprazole both as gastric antiseecretory agents and plasma gastrin elevating agents can be determined by

a pharmacological study in animals according to the method of Decktor et al. [J. Pharmacol. Exp. Ther. 249, 1-5 (1989)]. The test provides an estimate of relative activity, potency and, through a measure of specificity, an estimate of therapeutic index.

5 Fasted rats, implanted with a gastric cannula, receive single oral or parenteral doses of (+) lansoprazole, (-) lansoprazole or racemate, 1 hour before collection of gastric juice over a four hour

10 period. Acid output and pH are then determined on each sample. Dose response evaluations are performed with each compound to determine the lowest dose which inhibits acid output by at least 95% and maintains gastric pH above 7.0. Plasma gastrin levels are then

15 determined in a second group of rats treated with the doses selected in the first series of tests. Blood samples are taken for analyses over the five hour period after dosing, and both peak level as well as area-under-the-curve analyses of the gastrin

20 responses are made. These responses are then analyzed statistically using Student's "t" test to assess whether equivalent antisecretory doses show differences in gastrin responses.

Any suitable route of administration may be

25 employed for providing the patient with an effective dosage of (-) lansoprazole. Rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, topical and like forms of administration are possible; oral administration is preferred. Oral

30 dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, and the like.

The pharmaceutical compositions of the present invention comprise (-) lansoprazole as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic bases. Since the compound of the present invention is a weak acid and is unstable at low pH, salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic and organic bases. Suitable pharmaceutically acceptable base addition salts for the compound of the present invention include metallic salts of aluminum, calcium, lithium, magnesium, potassium, sodium, titanium and zinc or organic salts made from lysine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. If any salt is to be used, sodium salts are preferred.

The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations. It has been

found that the inclusion of basic salts of calcium and magnesium in the compositions allows the preparation of tablets and capsules having lansoprazole in a non-salt form and yet retaining
5 good stability. If desired, tablets and granules may be coated by standard aqueous or nonaqueous techniques. Oral dosage forms suitable for lansoprazole are described in US patent 5,035,899 and in PCT applications WO96/01624, WO97/12580 and
10 WO97/25030, the disclosures of which are incorporated herein by reference.

In addition to the common dosage forms set out above, the compounds of the present invention may-----
also be administered by controlled release
15 formulations, which are well known in the art. Compositions suitable for rectal administration are described in European Application 645140, the disclosure of which is incorporated herein by reference.

20 Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or
25 granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of
30 bringing into association the active ingredient with the carrier which constitutes one or more necessary

ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if
5 necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be
10 prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by
15 molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 5 mg to about 180 mg of the active ingredient, and each cachet or capsule contains from about 5 mg to
20 about 180 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains one of three dosages: about 15 mg, about 30 mg or about 60 mg of (-) lansoprazole for oral administration.

25 The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many
30 modifications, both to materials and methods, may be practiced without departing from the purpose and

interest of this invention.

EXAMPLES

Example 1 - Tablets

Composition per tablet:		
5	S(-) lansoprazole	30 mg
	Precipitated calcium carbonate	50 mg
	Corn Starch	40 mg
	Lactose	73.4 mg
	Hydroxypropylcellulose	6 mg
10	Magnesium stearate	(0.05 ml)
	Total	200.0 mg

EXAMPLE 1

S(-) Lansoprazole, precipitated calcium
15 carbonate, corn starch, lactose and
hydroxypropylcellulose are mixed together, water is
added, and the mixture is kneaded, then dried in
vacuum at 40° C. for 16 hours, ground in a mortar and
passed through a 16-mesh sieve to give granules. To
20 this is added magnesium stearate and the resultant
mixture is made up into tablets each weighing 200 mg
on a rotary tableting machine.

Example 2 - Granules

Composition per tablet:		
	S(-) lansoprazole	30 mg
	Magnesium carbonate	20 mg
5	Corn Starch	80 mg
	Microcrystalline cellulose	20 mg
	Carboxymethylcellulose calcium	10 mg
	Hydroxypropylcellulose	10 mg
	Pluronic F68	4 mg
10	Lactose	26 mg
	Water	(0.05 ml)
	Total	200 mg

EXAMPLE 2

- 15 The ingredients above are mixed well in the proportions shown, water is added, and the mixture is kneaded and granulated in an extruder granulator (screen size 1.0 mm ϕ). The granules are immediately converted to spherical form in a spheronizer. The
- 20 spherical granules are then dried under vacuum at 40° C. for 16 hours and passed through round sieves to give 12- to 42-mesh granules.

Example 3 - Capsules

Enteric coating composition:

5	Eudragit L-30D	138 mg (solids 41.4 mg)
	Talc	4.1 mg
	Polyethylene glycol	
	5000	12.4 mg
	Tween 80	2.1 mg
	Water	276 μ l

Composition of enteric granules:

Granules of Example 5	200 mg
Enteric coat	<u>60 mg</u>
Total	260 mg

Composition per capsule:

15	Enteric granules	260 mg
	No. 1 hard capsule	<u>76 mg</u>
	Total	336 mg

EXAMPLE 3

20 Enteric granules are produced by coating the granules obtained in Example 2 with the enteric coating composition shown using a fluidized bed granulator under conditions such that the inlet air temperature is 50° C. and the granule temperature is
25 about 40° C. Number 1 hard capsules are filled with the enteric granules thus obtained in an amount of 260 mg per capsule using a capsule filling machine.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to the
30 excipients or to the final weight of the tablet. An enteric coating, such as the polyacrylate Eudragit L® and Eudragit S® series, is applied by spray coating the tablets, preferably with an aqueous dispersion of the coating polymer.

What is claimed is :

1. A method of treating ulcers with
lansoprazole which comprises administering to a human
a therapeutically effective amount of optically pure
S(-)isomer of lansoprazole, or a pharmaceutically
5 acceptable salt thereof.

2. A method of treating gastroesophageal
reflux disease which comprises administering to a
human a therapeutically effective amount of optically
pure S(-)isomer of lansoprazole, or a
5 pharmaceutically acceptable salt thereof.

3. A method of treating a condition caused by
or contributed to by gastric hypersecretion which
comprises administering to a human a therapeutically
effective amount of optically pure S(-)isomer of
5 lansoprazole, or a pharmaceutically acceptable salt
thereof.

4. The method according to claim 3 wherein
said condition is Zollinger-Ellison Syndrome.

5. A method of treating psoriasis which
comprises administering to a human a therapeutically
effective amount of optically pure S(-)isomer of
lansoprazole, or a pharmaceutically acceptable salt
thereof.

6. The method of any of claims 1-5 wherein (-)
lansoprazole is administered orally.

7. The method of claim 6 wherein the amount of (-) lansoprazole or a pharmaceutically acceptable salt thereof administered is from about 5 mg to about 180 mg per day.

8. The method of claim 7 wherein the amount administered is from about 10 mg to about 60 mg per day.

9. The method of any of claims 1-5 wherein the amount of (-) lansoprazole or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total weight of lansoprazole.

10. The method of any of claims 1-5 wherein the amount of (-) lansoprazole or a pharmaceutically acceptable salt thereof is greater than approximately 99% by weight of the total weight of lansoprazole.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier for oral therapy and a therapeutically effective amount of (-) lansoprazole or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer.

12. A pharmaceutical composition according to claim 11 in the form of a tablet or capsule.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/01920

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44

US CL :514/338

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, HCAPLUS, USPATFULL- lansoprazole and isomers for the treatment of ulcers and GI hypersecretion disorders as well as psoriasis.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database USPATFULL on STN, AN 1998:54520, WO 9601624, BERGSTRAND et al., Multiple Unit Pharmaceutical Preparation. abstract, 25 January 1996.	1-12

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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